ORIGINAL ARTICLE

The Treacher Collins Syndrome

A Clinical, Radiological, and Genetic Linkage Study on Two Pedigrees

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Background: The Treacher Collins syndrome (TCS) is an autosomal dominant hereditary syndrome with variable penetrance and expression. The clinical characteristics are the result of dysmorphogenesis of the first and second embryonal branchial arch systems. The gene responsible has been located on the long arm of chromosome 5. Treacher Collins syndrome is rare, and in 60% of the patients the family history is negative. Consequently, only a few family studies are available. This renders it difficult to make a diagnosis and to comply with the increasing demand for genetic counseling. To gain insight into the diagnosis and variation in expression and penetrance of TCS, a clinical study was started followed by gene linkage research.

Methods: Audiological and physical tests were performed on 59 persons belonging to two families. In selected cases (n=19), vestibular and radiological examinations were also conducted. Blood samples were taken from 55 persons for gene linkage studies.

Results: The diagnosis of TCS could be made in 13 persons after clinical examination. The radiological detection of zygomatic hypoplasia or aplasia played an important supportive role. In addition to the 13 persons with TCS mentioned above, gene linkage studies showed positive linkage to chromosome 5q32-33.2 in three persons with clinical nonpenetrance.

Conclusions: This is the first time nonpenetrance of TCS has been demonstrated convincingly. In individual cases, clinical examination alone cannot always remove doubts about the diagnosis. Therefore, gene linkage studies will play a decisive role. Identification of the gene responsible for TCS is expected to be very useful in clinical practice.

(Arch Otolaryngol Head Neck Surg. 1995;121:509-514)

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THE TREACHER Collins syndrome (TCS), or mandibulofacial dysostosis, is an autosomal dominant inherited syndrome (MIM [mendelian inheritance in man] No. 154500). The typical features of TCS, summarized in **Table 1**, are the result of bilateral morphogenetic disruption of the first and second branchial arches.[1,2] Recently, however, unilateral and asymmetrical aspects have been emphasized by Wilkinson and Poswillo.[2] The gene for TCS is localized on the long arm of chromosome 5.[3] Treacher Collins syndrome is thought to arise as the result of a de novo mutation in 50% to 60% of cases.[1] The incidence is estimated to range from 1 in 40 000 to 1 in 70 000 live births.

Penetrance is thought to be almost 100%. Only occasional cases where nonpenetrance is suspected have been documented.[4] In most cases of suspected TCS, careful examination of the obligate carrier frequently reveals minor stigmata of TCS. Mandibulofacial dysostosis bears many eponyms, originating from original contributions by Thomson (1847),[5] Berry (1889),[6] Treacher Collins (1900),[7] Franceschetti and Zwahlen (1944),[8] and Franceschetti and Klein (1949).[9] The English-language literature prefers "Treacher Collins syndrome" as an eponym for mandibulofacial dysostosis. In cases with full expression of the syndrome (**Figure 1**), TCS can be diagnosed easily on the basis of the clinical appearance. Consequently, genetic counseling can be given without any reticence. However, if only minor stigmata are present, diagnosis and the provision of genetic counseling become more difficult.

The value of genetic linkage studies for individual genetic counseling

See Methods on next page

METHODS

A clinical study was launched involving two families (A and B); all the family members were asked to cooperate via the probands (**Figure 2**). All subjects underwent detailed otorhinolaryngological assessment. All subjects were tested audiologically by pure-tone audiometry at frequencies from 0.25 to 8 kHz.

If TCS was diagnosed or if there was any doubt about the diagnosis of TCS, radiodiagnosis was added to the clinical examination. This consisted of an occipitomental projection of the skull (Waters' view, posteroanterior with the canthomeatal line extended 45°, with no inclination of the incident ray) and an orthopantogram.

Special attention was paid to hypoplasia or aplasia of the zygomatic arch, changes in the mandible, and temperomandibular joint abnormalities.

All the subjects (except for case III-13 from family A) who had a diagnosis of TCS based on clinical and radiodiagnostic examination underwent vestibular tests with electronystagmography. Two subjects (cases II-2 and III-10 from family A) were added to this group because it was obvious that their children were affected. All the cases (n=14) were examined for evoked nystagmus and spontaneous nystagmus in the dark. Smooth-pursuit eye movements were tested, followed by optokinetic nystagmus tests. The vestibulo-ocular reflex was evaluated using velocity step tests. Caloric tests were performed only in case IV-1 from family B.

Blood samples were taken from 55 family members (except for cases IV-18, IV-19, IV-25, and V-1 from family A) for genetic linkage studies. Methods, analysis, and results of this part of the study have been reported in detail elsewhere.[10]

Table 1. Features of the Treacher Collins Syndrome

	Frequency, %
Antimongoloid slanting of the eyes	89
Coloboma, frequently combined with absence of eyelashes on the medial part of the lower eyelid	69
Hypoplasia or aplasia of the zygomatic arch	89
Malar hypoplasia	81
Mandibular hypoplasia	78
Pinna dysplasia	77
Conductive deafness, middle ear malformations	50
Meatal atresia	36
Cleft palate	28
Preauricular hair prolongation	26
Absence of lower lacrimal puncta	?
Ear appendages, preauricular sinus	?
High arched palate	?
Macrostomia, malocclusion	?
Nearly missing nasofrontal angle	?
Obstructive sleep apnea syndrome	?
Choanal atresia	?

Figure 1. *Typical appearance of a patient with Treacher Collins syndrome (case IV-30 from family A).*

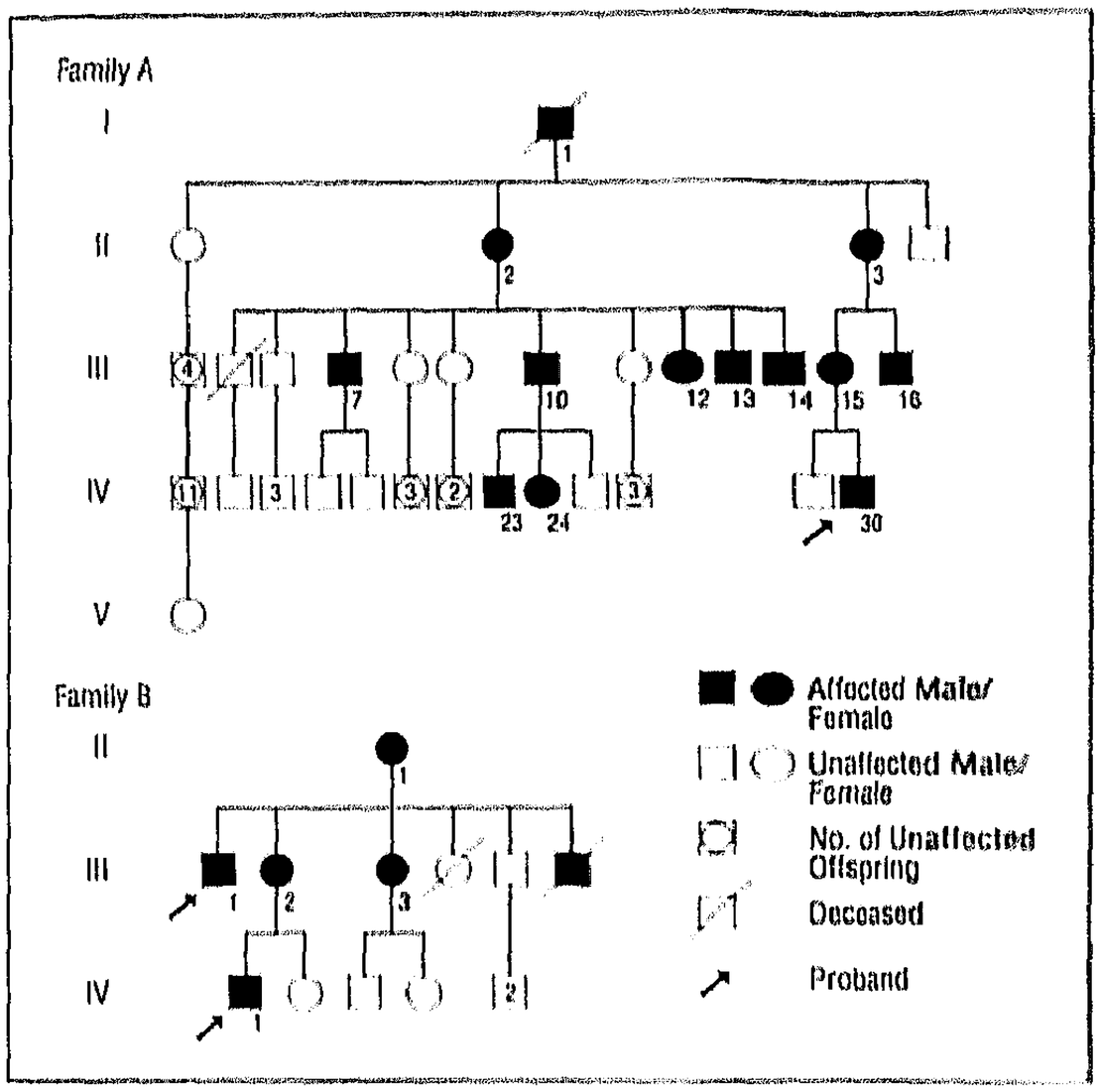

Figure 2. *Pedigrees of family A and family B. All family members cooperated in this study except for case III-1 from family B. Case IV-1 from family A died in early childhood.*

was assessed by performing a clinical study on two families with remarkable variation in TCS.

RESULTS

A total of 59 persons from both families participated in this study. One other person known to have TCS (case III-1 from family B) was unable to participate.

Clinical examination revealed that nine persons were affected with TCS (cases II-3, III-12, III-13, III-15, III-16, IV-24, and IV-30 from family A and cases II-1 and IV-4 from family B). Five persons had only minor stigmata of TCS (cases III-7, III-14, IV-2, IV-4, and IV-5 from family A). It was not possible to make the diagnosis of TCS in six persons via clinical examination, although TCS had been demonstrated or was initially suspected in their offspring (cases II-1, II-2,

III-2, and III-10 from family A and cases III-2 and III-3 from family B) (**Figure 3**). Therefore, a total of 14 persons did show (minor) stigmata of TCS, and nonpenetrance was initially suspected in six persons. The features are summarized in **Table 2**.

In the remaining group of 39 nonaffected persons who underwent clinical examination and audiometry, three persons showed abnormalities that were not thought to be related to TCS. Cases IV-9 and IV-21 from family A had bilateral commissural lip pits, and case III-11 had an unexplained sensorineural hearing loss (30 dB in the right ear and 25 dB in the left ear, pure-tone average). This normal group was excluded from further radiological or vestibular assessment.

Figure 3. *Case III-2 (left) and case III-3 (right) from family B. Although both cases were affected, no stigmata of the Treacher Collins syndrome can be seen. However, aplasia of the zygomatic arches was demonstrated by Waters' projection.*

RADIOLOGY

Conventional roentgenograms consisting of a Waters' projection were initially taken in 18 persons (**Table 3**). In two persons (cases III-2 and III-3 from family B), the diagnosis of TCS was strongly supported by the outcome of the Waters' projection; aplasia (discontinuity) of the zygomatic arch was visible, in contrast to their facial appearance, which showed no signs of it (digital palpation was not performed). In two other cases (cases III-7 and III-14 from family A) with suspected TCS, the diagnosis could be confirmed radiologically. In six cases (cases II-1, II-2, III-2, III-10, IV-4, and IV-5 from family A) in whom the diagnosis of TCS could not be made on clinical grounds alone, no abnormalities could be demonstrated radiologically. The clinical diagnosis of TCS was made in nine cases, as mentioned before, and eight of these patients underwent radiological assessments; in all of these cases aplasia (discontinuity) of the zygomatic arch was present (**Figure 4**).

Temporomandibular joint abnormalities were found in four cases, all of whom also had zygomatic arch aplasia (Table 3). Concavity of the mandibula was present in six cases and corresponded with other radiological signs of TCS in five cases. Asymmetrical changes of TCS were found on conventional roentgenograms in two cases.

The combination of clinical examination and radiological assessment provided a diagnosis in only 13 cases. Two other cases without any clinical or radiological signs of TCS (cases II-2 and III-10 from family A) could be added to the group with TCS because of their affected offspring. In five other cases with minimal stigmata, the diagnosis of TCS could not be excluded with certainty.

Table 2. Features of the Treacher Collins Syndrome Present in Families A and B*

Case No./ Sex/ Age, y	Anti-mongoloid Slanting	Coloboma	Malar Hypoplasia	Mandibular Hypoplasia	Aplasia Zygomatic Arch	High-Arched (HA) or Cleft (C) Palate	Preauricular Sinus	Pinna Dysplasia	Meatal Atresia	Hearing Loss, dB†
					Family A					
II-1/F/81	—/—	—/—	—/—	—	—/—	—	—/—	—/—	—/—	—/—
II-2/F/80	—/—	—/—	—/—	+	—/—	—	—/—	—/—	—/—	50/60
II-3/F/79	+/+	±/±	+/+	+	+/+	—	—/—	—/—	—/—	80/95
III-2/F/56	—/—	—/—	—/—	—	—/—	HA	—/—	—/—	—/—	—/—
III-7/M/49	—/—	—/—	—/—	+	+/+	HA	—/—	—/—	—/—	—/—
III-10/M/45	—/—	—/—	—/—	—	—/—	—	—/—	—/—	—/—	50/15
III-12/F/43	—/—	±/—	+/+	+	+/+	HA	—/—	—/—	—/—	—/—
III-13/M/41	+/+	+/+	+/+	+	+/+	—	—/—	—/—	—/—	—/—
III-14/M/37	—/—	±/±	—/—	+	+/+	HA	+/—	—/—	—/—	20/30
III-15/F/49	—/—	—/—	+/+	+	+/+	HA	—/—	—/—	—/—	25/20
III-16/M/47	+/+	+/+	+/+	+	+/+	HA	—/—	—/—	—/—	50/60
IV-2/F/26	—/—	—/—	±/±	+	—/—	HA	—/—	—/—	—/—	—/—
IV-4/M/24	—/—	—/—	—/—	—	—/—	HA	+/+	—/—	—/—	—/—
IV-5/M/21	—/—	—/—	—/—	—	—/—	HA	+/+	—/—	—/—	—/—
IV-24/F/12	+/+	—/—	+/+	+	+/+	HA	—/—	—/—	—/—	—/—
IV-30/M/20	+/+	+/+	+/+	+	+/+	HA	+/+	+/+	+/+	60/55
					Family B					
II-1/F/69	+/+	+/+	+/+	+	+/+	HA	—/—	+/+	+/—	90/50
III-2/F/42	—/—	—/—	—/—	—	+/+	—	—/—	—/—	—/—	—/—
III-3/F/41	—/—	—/—	—/—	—	+/+	—	—/—	—/—	—/—	—/—
IV-1/M/19	+/+	+/+	+/+	+	+/+	C	—/—	—/—	—/—	50/50

**In most columns, values are given by sides as "right"/"left"; minus sign indicates not present; plus sign, present; and plus-or-minus sign, mild.*
†Values are pure-tone averages at the following frequencies: 0.5, 1.0, and 2.0 kHz.

Table 3. Results of Clinical and Radiological Examinations*

Case No./ Sex/ Age, y	Clinical Diagnosis	Hearing Loss	Zygomatic Arch	Concavity	Abnormality in Temporomandibular Joint	Radiological Diagnosis	Remarks
				Family A			
II-1/F/81	–	–	N	–	–	–	
II-2/F/80	–	+	N	–	–	–	
II-3/F/79	+	+	NP	NP	NP	NP	Discomfort
III-2/F/56	–	–	N	–	–	–	
III-7/M/49	?	–	Aplasia	+	+	+	
III-10/M/45	–	+	N	–	–	–	
III-12/F/43	+	–	Aplasia	+	+	+	
III-13/M/41	+	–	Aplasia	–	–	+	
III-14/M/37	?	+	Aplasia	+	–	+	
III-15/F/49	+	+	Aplasia	–	–	+	
III-16/M/47	+	+	Aplasia	–	–	+	
IV-2/F/26	?	–	NP	NP	NP	NP	Pregnant
IV-4/M/24	?	–	N	+	–	–	
IV-5/M/21	?	–	N	–	–	–	
IV-24/F/12	+	–	Aplasia	+	+	+	Asymmetry
IV-30/M/20	+	+	Aplasia	NP	+	+	
				Family B			
II-1/F/69	+	+	Aplasia	–	–	+	
III-2/F/42	–	–	Aplasia	–	–	+	
III-3/F/41	–	–	Aplasia	+	–	+	
IV-1/M/19	+	+	Aplasia	–	–	+	Asymmetry

*Minus sign indicates no; N, normal; plus sign, yes; NP, examination not possible; and question mark, diagnosis uncertain.

AUDIOMETRY

Pure-tone audiometry revealed an elevated hearing threshold in nine of the 20 above-mentioned cases (Table 2). According to the medical history, a congenital cause was present in all cases except two (cases III-14 and III-15 from family A).

The air-bone gap (defined as the mean difference between the air-conduction and bone-conduction hearing levels at frequencies of 0.5, 1.0, and 2.0 kHz) ranged from 10 to 55 dB. A bone-conduction hearing level of more than 25 dB was noticed at some frequencies but especially at the higher frequencies (4.0 and 8.0 kHz) in 12 of 18 ears. After correction for age-related hearing loss, these ears still showed a relevant sensorineural hearing loss.

VESTIBULAR EXAMINATION

Spontaneous nystagmus of significant intensity (>6°/s) was not encountered in any of the cases with TCS. Gaze positions, saccadic and smooth-pursuit eye movements, and optokinetic nystagmus were normal in all cases. The caloric responses of the proband from family B were normal (16°/s from either side).

Case III-14 exhibited strong vestibular hyporeflexia that was close to areflexia. The cervico-ocular reflex, tested in darkness (eyes open) by sinusoidal rotation of the trunk under the head fixed in space at an amplitude of 30° and a period of 10 seconds, showed enhancement typical of that found in subjects with a labyrinthine defect.

Hyperreflexia of the velocity step responses was found in five cases (cases II-3, III-15, and III-16 from family A and cases II-1 and II-12 from family B).

GENE LINKAGE STUDIES

Positive gene linkage could be demonstrated in 16 of the 55 samples.[10] None of the five cases in whom it was not possible to exclude the diagnosis of TCS with certainty showed positive linkage. However, positive gene linkage was demonstrated in the two cases with affected offspring (cases II-2 and III-10 from family A), as expected. Surprisingly, one other person in whom TCS was not suspected at all showed positive gene linkage (case IV-23 from family A) (**Figure 5**). Additional roentgenograms of this case did not show any abnormalities, and the hearing thresholds were normal.

The combination of clinical and radiological assessments and gene linkage analyses demonstrated that 16 persons were affected with TCS. Based on the clinical examination alone, TCS was initially suspected in only nine of these cases.

COMMENT

The extensive variation in expression of TCS is supported by the classification suggested by Franceschetti and Klein,[9] who distinguished between complete, incomplete, abortive, unilateral, and atypical forms. In our opinion, it would be better to discriminate on the basis of full expression or mild expression. Full expression comprises at least the following features: antimongoloid slanting of the eyes, coloboma, and hypoplasia of the facial bones. If this triad is not present, we consider the patient to show mild expression. The unilateral and atypical forms described by Franceschetti and Klein have

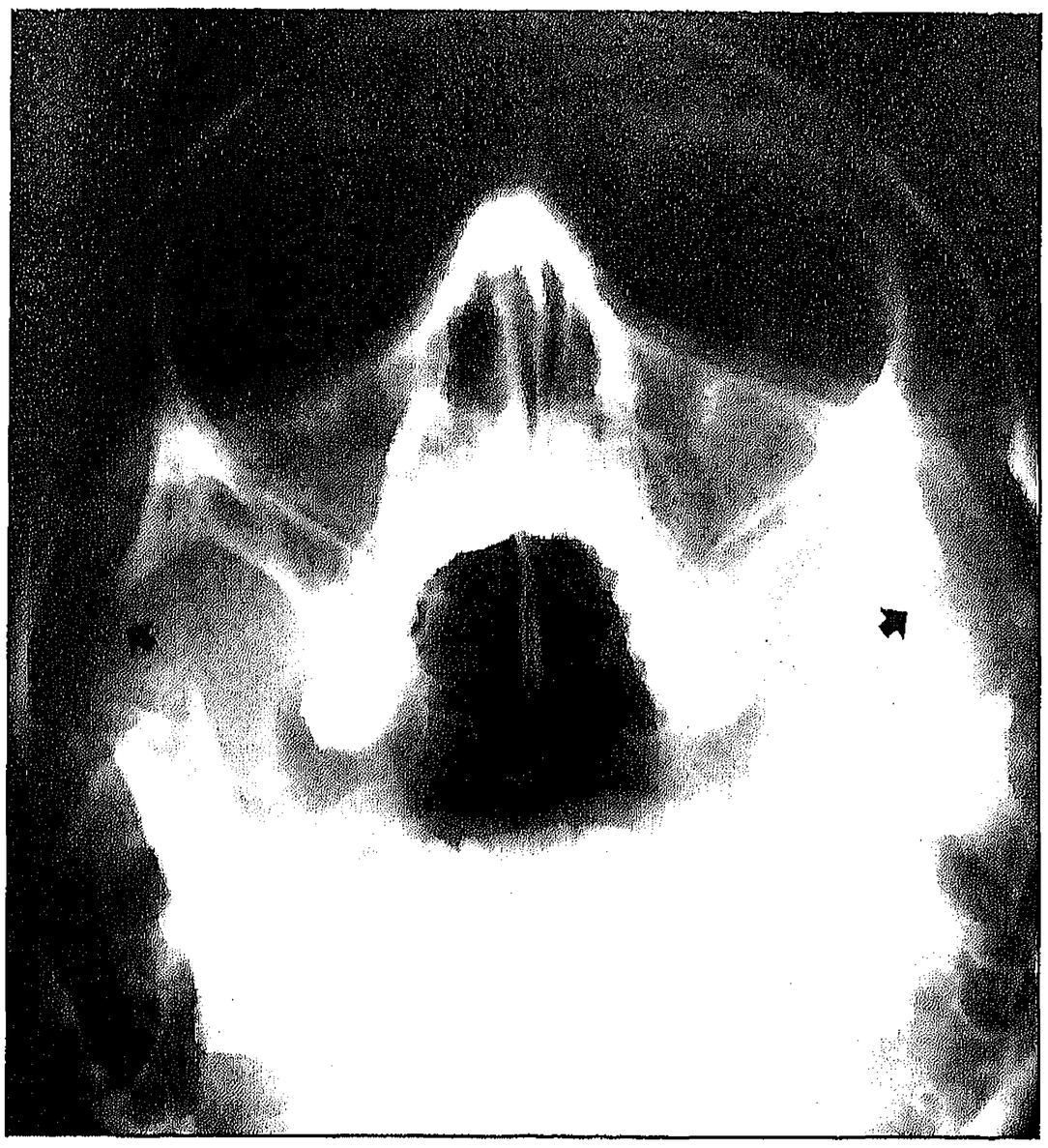

Figure 4. *Aplasia of zygomatic arches on Waters' projection in case III-12 from family A (arrows).*

features that make a diagnosis within the oculoauriculovertebral spectrum more suitable.

In cases where only minor stigmata are present, diagnosis and additional genetic counseling are more difficult. To detect such cases with minor expression of TCS, two Dutch families were invited to undergo selective clinical and radiological investigation combined with gene linkage studies. During clinical examination, we noted remarkable differences in the extent or variation of expression within these two families. Radiodiagnostic tests proved particularly useful to confirm the diagnosis in cases in whom mild expression was suspected on clinical grounds. We chose two simple radiological examinations that avoided discomfort for the participants and required a minimum of radiation. The most common abnormality and the one most easily recognizable radiologically was zygomatic arch hypoplasia or aplasia. Orthopantograms can be used to demonstrate mandibular hypoplasia (which is difficult to quantify) and changes in mandibular configuration. Temporomandibular joint abnormalities and asymmetry can be assessed on the same films.

To our knowledge, there are no reports in the literature on the radiological screening of persons at risk for TCS, but a simple Waters' view has proved sufficient to detect zygomatic arch hypoplasia in patients with a diagnosis of TCS.[11] In the present study, the diagnosis of TCS could be confirmed radiologically in all the clinically suspected cases. Furthermore, two additional cases with zygomatic arch abnormalities were detected and TCS was diagnosed mainly on the basis of the radiological examination results. Other features, such as temporomandibular joint abnormalities and mandibular hypoplasia, were seen less frequently, but we were unable to quantify them because of the method used in this study.

Figure 5. *Case IV-23, with nonpenetrance of the Treacher Collins syndrome.*

Radiological examination also revealed bony asymmetry in a number of cases, particularly those with less serious expression of TCS. Similar findings have been reported in other studies, but usually in cases with full expression of the syndrome.[1,12]

Whenever a patient needs any form of surgical treatment, computed tomographic scanning is obligatory. Audiological examination of patients with TCS is important because about 50% have hearing loss. This is nearly always conductive hearing loss resulting from an ossicular chain anomaly, alone or in combination with aural atresia. Reconstructive surgery is not recommended before the age of 10 years.[13] Some forms of aural atresia are not suitable for surgery.[13]

The sensorineural component in the hearing loss of a few of the above-described cases was unusual, but similar findings have occasionally been reported in other studies.[14-16] There is no explanation for this phenomenon, although some earlier studies described histopathological anomalies of the inner ear.[17,18] One would expect to encounter such findings in cases with the more serious form of TCS, not in the less seriously affected cases.

The finding of vestibular hyperreactivity can be explained in terms of false-positive results. According to statistical analysis, this finding was not significant. In the literature, only an occasional case report presents the results of vestibular investigation of TCS cases, but neither hyporeflexia nor hyperreflexia is mentioned.[9,19,20]

An important observation in this study is that there is no impairment of the vestibulo-ocular reflex in TCS. This is contrary to the findings in cases with the branchio-oto-renal (BOR) syndrome, who do have hypofunctioning.[21] Sensorineural or mixed hearing loss is also observed more frequently in patients with the branchio-oto-renal syndrome.

In cases with TCS suspected on the basis of clinical and/or radiological findings, the diagnosis could be confirmed with the aid of gene linkage studies. The positive gene linkage finding in case IV-23 was a surprise and constitutes a clinically relevant observation, because nonpenetrance of TCS has never before been demonstrated with such clarity.

In addition, cases II-2 and III-10 from family A demonstrated positive gene linkage and also nonpenetrance. However, the diagnosis of nonpenetrant TCS was suspected on clinical grounds because of the affected offspring of these two cases. Because of absence of any trait in these three cases, the diagnosis of TCS cannot be made. It would be better to consider them affected by the TCS gene.

A negative family history in 60% of cases with TCS was always thought to be acceptable. However, the results of the present study cause us to doubt this. This doubt can also be extended to the incidence of associated symptoms, listed in Table 1.

The occurrence of nonpenetrance and the fact that a number of affected cases had such mild expression is of great importance for genetic counseling regarding TCS. By making use of the gene linkage facilities currently available, it will be possible to achieve a greater level of accuracy in diagnosis.

Accepted for publication January 26, 1994.

This study was supported by a grant from the Monseigneur J. C. van Overbeek Foundation, Nieuwkuijk, the Netherlands.

The authors thank Annelies van Aarem, MD, Bas van den Borne, MD, and Jan Meeuwissen for their support during this study and Martin G. M. Nicolasen for carrying out the vestibular examinations and analyses.

The photographs that constitute Figure 1 were kindly provided by Hans-Peter M. Freihofer, MD, Department of Maxillofacial Surgery, University Hospital of Nijmegen.

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